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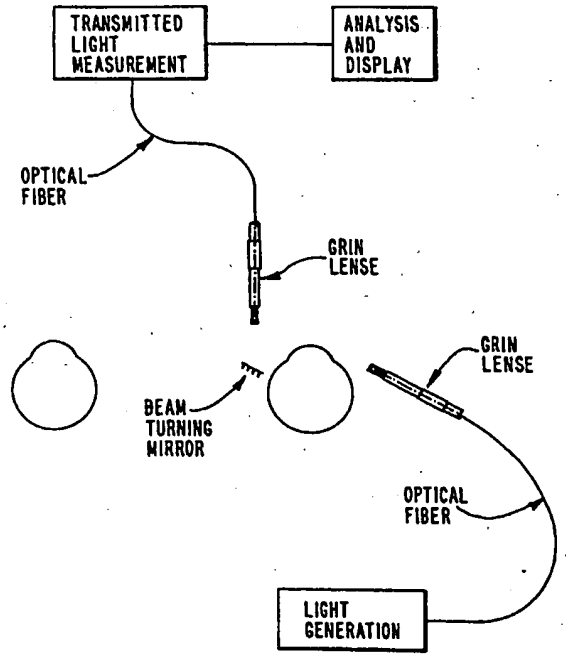
(57) Abstract

This invention relates to blood glucose measurement by hand held devices and by devices designed into vision glasses and that optically measure glucose concentration in the aqueous humor of the eye. The invention uses fiber optics and graded index (GRIN) lenses to precisely locate and direct an optical beam transversely through the cornea and aqueous humor to allow a precise measurement of the glucose concentration. Vision glasses in accordance with the invention contain components within their frames and allow continous blood glucose measurements.



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APPARATUS TO NON-INVASIVELY MEASURE GLUCOSE OR OTHER CONSTITUENTS IN AQUEOUS HUMOR USING INFRA-RED SPECTROSCOPY

Field of the Invention

The present invention relates generally to the measurement of blood solutes using spectrographic techniques. The invention relates more specifically to techniques for obtaining spectral measurements of aqueous humour contents in vivo to provide information about the glucose concentration.

Background of the Invention

Diabetes mellitus is a chronic disease of pancreatic origin that is characterized by insufficient insulin and excess glucose in the blood. There are many adverse effects on the body due to this disease and in severe cases blindness, amputation of limbs or even death may result if the disease is untreated. Fortunately, it is possible to replace the deficient insulin and the patient with this disease can lead a normal life if the insulin level is carefully managed.

The patient with a severe insulin deficiency must take insulin injections to supplement what the body produces. Insulin is a powerful hormone and too much can also be very dangerous, so the patient must measure the level of blood sugar (glucose) and adjust the volume of injected insulin accordingly. The present state of the art for patient self-monitoring uses a drop of blood obtained by puncturing the finger with a lancet, a "finger stick." This drop of blood is placed on reactive paper which changes color depending on the glucose level. The patient then compares the darkness of the color

change with a standard chart or uses a portable optical densitometer to measure the darkness which then permits adjustment of the insulin dosage.

The requirement for repeated finger sticks, up to four per day in severe cases, leads to reluctance on the part of the patient to make measurements as often as required, and the management of the disease becomes non-optimal. Other approaches to measurement of the glucose level have been tried to improve the management. One such approach uses an implanted monitor which can continuously monitor glucose levels.

These units work but have an operating lifetime of only seven to ten days before they must be replaced. The discomfort and inconvenience of this procedure has led to very low patient acceptance. Optical techniques making measurements through the skin have also been developed, but they have had poor results in achieving consistent measurement accuracy and have not been approved for use by the Food and Drug Administration.

Thus there is a need for a non-invasive (no finger stick or implanted sensor) measurement of blood glucose level that matches the accuracy of the current state of the art.

An alternative approach to these measurements is to measure the glucose level in the aqueous humor of the eye as described by U.S. Nos. 5,835,215, 5,433,197 5,535,743 5,258,788 and 4,014,321. The aqueous humor, which is close in composition to blood serum, provides nourishment and waste removal for the living cornea and lens in the eye. It is secreted by special cells within the eye and has been measured to have 80% of the glucose level of the blood serum. The glucose level in the aqueous humor has also been shown to rise in laboratory animals with induced diabetes. Since the cornea of the eye is highly transparent, it provides a window for optical measurements of the aqueous humor.

The aqueous humor is a low viscosity fluid that fills the space between the lens and cornea of the eye. It provides metabolic support for the lens and cornea but contains no cells because it must remain transparent for vision. The aqueous humor is closely related to both blood serum and cerebrospinal fluid in composition, the main differences being that the aqueous humor has a much lower protein concentration. In addition to the low concentration of protein, which is 6 to 7g/100ml in serum but less than 15mg/100ml in aqueous humor, the aqueous humor also has a very high relative concentration of ascorbate and a slightly higher concentration of lactate.

Although eye aqueous humor contains glucose, a satisfactory method or device for inferring blood glucose concentration from non-invasive testing of the aqueous humor has not been developed. As a result, present methods of blood glucose determination, and of diabetes status rely heavily on invasive testing.

Devices proposed by others in the above-cited patents generally utilize light that enters the front of the eye and is scattered or reflected back out the front. Such devices have not been commercially successful and suffer various drawbacks. One drawback is the danger of sending light directly into the retina. Among other things, this hazard prevents the use of even low power lasers to carry out a measurement. A reflectance measurement is adversely affected, for example by the conditions and changes to the structure that it is reflected from and which comprise a new source of error. Accordingly, a new method and devices are needed to exploit near infra-red absorbance by glucose in the aqueous humour to infer blood glucose level.

Summary of the Invention

Accordingly, it is the object of this invention to determine blood glucose level non-invasively. In particular, it is an object of this invention to determine blood glucose level from the aqueous humour of the eye without the problems of relying on indirect reflected light from deep inside the eye to obtain a measurement. Another object of the invention is to determine diabetes status and the long term glucose status of the body without having to physically contact or take a sample of blood.

In accomplishing these objectives, the invention provides an instrument that comprises an infra-red light source, a means to conduct the light from the source to the eye, a means for focusing the light as a parallel beam incident on the eye at a controlled position and angle of incidence, a means for collecting the light that leaves the eye, a means for detecting the intensity of the light collected and a means for processing and displaying the results.

In one preferred embodiment, two wavelengths are selected from the light source; one which is specifically absorbed by glucose and a nearby wavelength that is not absorbed by glucose. These two wavelengths are transmitted to the eye, and focused on the eye in such a way that they traverse the cornea at a first location and aqueous humor and exit through the cornea at a second location. The light from these two wavelengths is measured and quantified separately and the ratio of the signals is used as the measurement of glucose concentration. In one embodiment, glucose concentration is determined from a look-up table with a computer, such as a microprocessor. This technique removes uncertainties in light intensity and effects of absorption or scattering that may occur in the eye.

One embodiment of the invention is a device for measuring blood glucose, comprising an infra-red light source, a means for transferring light from the light source to the eye and for directing the transferred light through the cornea and aqueous humor of the eye, a light detector that receives the transferred light from the eye and that converts information from the light into an electrical signal, an electrical processor to convert the electrical signal into a value corresponding to blood glucose concentration, and a display to indicate the value.

In another embodiment, the sensor is a hand-held unit and in a further embodiment the sensor is incorporated into glasses. These and further embodiments will be readily appreciated by the skilled artisan upon reading the specification.

Brief Description of the Drawings

Figure 1 shows a drawing of a cross section of the human eye including the lens, iris and cornea. The broken line shows the centerline of a preferred optical beam path passing through the cornea and aqueous humor according to an embodiment of the invention.

Figure 2 shows a schematic view of all of the system elements and their relationship to the eye.

Figure 3 shows a table of absorption lines of glucose with wavelengths given in nanometers (nm). Lines which are most useful for the required measurements are identified.

Figure 4A is a diagram of a pair of fiber coupled GRIN lenses showing the production of a collimated beam.

Figure 4b shows a diagram of a lens-fiber assembly as a preferred embodiment.

Figure 5 shows the relative positions of optical components for the measurement of aqueous humor in the eye.

Figure 6 shows a hand-held instrument from the operator's vantage point. The forward portion of the housing is curved to fit around the subject's forehead to position the instrument for making a measurement.

Figure 7 is a view of a representative hand-held instrument from the front with a cover plate removed to show the location of modules within the housing. The details of the fiber optics and lenses are not shown in this drawing for simplicity.

Detailed Description of the Preferred Embodiments

The inventors have discovered that blood glucose levels can be inferred by measuring the glucose level in aqueous humor spectroscopically using light that is directly transmitted through the aqueous humour of the eyeball. The inventors took advantage of the properties of the aqueous humor and cornea in a method of tracking blood glucose concentration through optical measurements made on the aqueous humor through the cornea. The inventors unexpectedly discovered that direct transmission of light through the aqueous humour of the eyeball can be used for near infra-red measurements without having to rely on reflectance from structure(s) within the eye.

The best spectral wavelength range for making these spectroscopic measurements from the aqueous humor lies between 800 and 2500 nanometers (nm) because this spectral region combines relative transparency of the cornea and aqueous humor and absorption features of the glucose molecule. Figure 1 shows a cross sectional view of the eye in a horizontal plane and illustrates a preferred optical path for the measurement based on a seventy degree angle of incidence. In different contemplated embodiments, the incidence

angle is approximately (plus or minus up to 3 degrees) 60 degrees, 63 degrees, 66 degrees, 70 degrees, and 76 degrees. The approximate distance from the front of the lens to the front of the cornea according to embodiments typically is between 2 and 25 millimeters and preferably is 5 millimeters, so there is a clear path for the beam to pass through the aqueous humor.

Figure 2 shows a representative schematic diagram of a measurement system contemplated. The measurement begins with the light generation module. In one preferred embodiment, this is a broad band light source, such as an incandescent lamp, and appropriate filters and lenses to select two wavelengths and focus them into the optical fiber. Two wavelengths are used, one absorbed by glucose and another nearby wavelength that is not absorbed, to eliminate effects of other losses in the optical path. In a second preferred embodiment, the light source is a broad band light source with a prism or grating spectrometer that can switch transmission between the desired wavelengths. In a third embodiment, the light source is a narrow band tunable source, such as a laser diode, that can be tuned between the two desired wavelengths. In a fourth embodiment, the light source may be broad band without any wavelength selection and the wavelength selection function may be performed exclusively by the detection system discussed in subsequent paragraphs of this disclosure. This approach has the advantage of simplicity and the disadvantage of subjecting the eye to larger light intensity than is required for the measurement. Others skilled in the field will be able to construct other mechanisms for generating light appropriate to this measurement.

The optical fiber is used to conduct the light from the light generating unit to the lens assembly that focuses the light onto the cornea of the eye. This is the preferred embodiment since it allows the light generation module to be located away from the lens

system. One skilled in the field will realize that it would be possible to integrate together the light generating unit and the focusing lens and eliminate the optical fiber at the cost of a larger, heavier unit mounted near the eye.

In one preferred embodiment the lens that focuses the light wavelengths onto the eye is a gradient index (GRIN) lens since this lens is compact, easy to couple to optical fiber and has very close tolerances on axial alignment making it easy to align with the eye. Others skilled in the art will realize that other lens systems, including discrete glass lenses and diffractive lenses can also be use to accomplish this purpose.

The beam turning mirror is placed near the "comer" of the eye on the bridge of the nose to re-direct the optical beam emerging from the eye to a forward direction. This is the preferred embodiment since the space between the eye and nose is limited and does not allow for safe placement of lenses or optical detectors.

In the preferred embodiment, the light beam leaving the turning mirror is collected by a second GRIN lens and coupled into an optical fiber. As with the first GRIN lens, one skilled in the art will realize that other systems of lenses or mirrors could be used to accomplish this task.

Also in the preferred embodiment, the light signal is conducted by an optical fiber from the second GRIN lens to a light measurement module. In the preferred embodiment, the light beam is separated into two wavelengths by use of appropriate optical filters and lenses and their intensities are measured by two separate optical detectors. In a second preferred embodiment, the light beams are alternatively switched on the same detector by using a rotating mirror or prism. This alternative approach has the advantage of eliminating any variation in sensitivity between the two detectors at the added complexity of the optical switching device. The optical measurement system converts the two optical

signals to two electrical signals, each of which is proportional to the intensity of one of the optical signals.

The analysis and display module processes the electrical signals and displays the result as a number representing the measured glucose concentration. In the preferred embodiment, the numerical value of the glucose-absorbed wavelength is divided by the numerical value of the unabsorbed wavelength, then multiplied by a calibration factor before display. This method is designed to eliminated effects of variation in light source intensity, optical coupling efficiencies and transmission by the cornea of the eye, and only represent effects due to glucose concentration. Others skilled in the art will be able to apply other signal processing techniques well known in the field of optical absorption spectroscopy.

The aqueous humor is formed by the cells of the ciliary epithelium lying behind the iris. Due to the composition of the humor, it may be concluded that it is not simply formed by a filtration process but is a secretion since osmotic work must be performed to make the aqueous humor from blood. Small molecules, such as glucose molecules, may enter the humor by diffusion and there is evidence that elevated blood glucose levels lead in turn to elevated glucose levels in the aqueous humor. The aqueous humor flows across the lens and through the iris to the anterior chamber behind the cornea and finally drains through the canal of Schlemm. It is difficult to measure the formation rate of aqueous humor without upsetting the pressure balance within the eye. Various techniques of monitoring penetration of substances into and out of the eye have been used, as well as radioactive tracers. A reasonable estimate of the turnover rate of aqueous humor is about 1.5% per minute (2), which would say that the aqueous humor is replaced about once per

hour. Based on these characteristics, it is possible to monitor the glucose level in the aqueous humor to provide a highly correlated measurement of the blood glucose level.

Positioning of the device for measuring transmission of light through the aqueous humour is carried out, in a preferred embodiment, in two steps. Step one is to position the eye relative to the head and eye socket. In a preferred embodiment, a small point light source and lens (to render the light rays parallel) is placed to allow the subject to look at the light source. With appropriate choice of lens, the light source is placed close to the eye and attached to the measurement apparatus.

Step two is to position the measurement light source, lenses and detector at the proper location with respect to the eye. This preferably is accomplished with array(s) of detectors positioned to detect both the transmitted and reflected beams from the light source. The reflected beam(s) is used to make sure that the incident beam strikes the correct location on the cornea, and the transmitted beam is used to make sure that the angle with respect to the normal to the cornea is correct.

In the preferred embodiment the light source and detector are both coupled to lenses using fiber optics so that only the lenses need to be positioned and the light source and detector may remain stationary. The flexible nature of the optical fiber permits the light to be guided to and from the lenses with very low loss. The signals from the detector array(s) are sent to a computer, which can deliver control signals to a servo system that mechanically adjusts lens position. In a preferred embodiment, the servo system is a piezo-electric transducer that is mounted along with the lens in headgear that comprises the light source and detectors. Such servo mechanisms are well known in the art and generally use small stepping motors and screw drives to accurately position optical components. Piezo-electric elements also are known to be usable for positioning optical

components. In another embodiment, an array of light sources and an array of detectors are used instead of a mechanical device and the adjustment is carried out by switching to a different light source/and or detector to compensate for changes in distance and angle with the eye surface.

The optical properties of corneas may differ among different subjects depending on age and medical condition. These effects are compensated for independently of glucose concentration in the aqueous humour by measuring the optical transmission and refection properties of the cornea at wavelengths that are not affected by glucose absorption. In one embodiment, wavelengths from the light source are scanned in the visible and near infra-red and data obtained is used to calculate the transmission of the cornea. The cornea transmission is used to correct for the cornea's effect on the glucose measurement. Measuring transmission at different wavelengths is a known method for determining different properties of a material from a single wavelength scan and the use of such methods is preferred to correct for variations due to cornea, positioning and the like in making a glucose measurement. One preferred analysis technique is to use partial least squares analysis.

In a preferred embodiment calibration of an instrument is carried out by measuring blood glucose concentration over an extended time (for example, 30 measurements over a one month period) with a reference method and, at the same time, with an instrument according to the invention, on the subject. The two sets of values are compared to calibrate the instrument to the specific user.

Optical Characteristics of the Aqueous Humor and Cornea.

The optical elements of the eye, including the cornea, lens and humors, have remarkable optical transparency, especially in the visible portion of the spectrum where, from 400 to 700 nm, the eye has a smooth transmittance with no absorption features. Beyond the visible wavelengths, both in the ultraviolet and in the infra-red, there are strong absorption features, but particularly in the near infra-red there are again regions of strong transmittance. Of particular interest for the invention is the spectral transmittance of the aqueous humor. This tissue exhibits high transmittance in the regions from 700 to 1300 nm, from 1600 to 1800 nm, and from 2100 to 2350 nm. These regions should be available for spectroscopic analysis.

Figure 3 lists some of the observed absorption lines from glucose. It is readily seen that some of the absorption lines of glucose fall within the normal transmittance windows of the aqueous humor so that, at higher spectral resolution, these absorptions appear as sharp features in the transmitted light.

In initial laboratory measurements the inventors scanned the entire spectrum and identified the strongest absorption lines without nearby interference from other constituents of the aqueous humor. The strength of the absorption line was calibrated with standard concentrations of glucose in water. In a portable system differential spectroscopy is most useful for calibration, however. This technique uses one filter to detect an absorption line, and a second nearby filter in a non-absorption portion of the spectrum. The ratio of the transmitted signals is then used to measure concentration. The advantage of this technique is that the non-absorbed reference line accounts for any other optical losses in the path and the ratio of the two signals measures only the absorption loss.

Optical Path

Figure 2 shows a cross sectional view of a portion of the eye including the cornea and aqueous humor. The eye itself is roughly spherical in shape with a diameter of approximately 25 mm. The cornea is a second spherical section at the front of the eye with diameter of approximately 17 mm. To make the desired measurement, a beam of light was projected through the aqueous humor parallel to the front face of the lens, and the transmitted beam was detected. The path preferably is parallel to the line defined by the eyebrow ridge and in one embodiment is determined by the wearing of glasses that contain the instrument for making a light transmission measurement. The broken lines in the figure show the optical path required. The clearance between the inside surface of the cornea and the plane defined by the iris is about 2.5 mm and the distance across the path is between 4 and 5 mm so there is adequate volume for the 1mm beam needed and the absorption path length of 4 to 5 mm is adequate for the measurement.

The eye has evolved with an optical design to bring all of the light striking the cornea from the forward direction into focus on the cornea. In the ideal case light is sent through the cornea and aqueous humor without striking the lens. The optical path shown is constructed using Snell's Law,

$$n_1 \sin(\Theta_1) = n_2 \sin(\Theta_2)$$

where n_1 and n_2 are the refractive indices of the two media that constitute a refractive surface and Θ_1 and Θ_2 are the angles measured from the normal to the refractive surface.

For the indices of refraction the inventors used 1.35 for the aqueous humor and 1.44 for the cornea, which is a value that has been measured for the lens. There is relatively little refractive power at the interface between the aqueous humor and the cornea since the indices of refraction are nearly the same. Most of the refraction occurs at the

air-cornea interface. As the drawing shows, the light must initially strike the cornea at approximately a 70 degree angle relative to the normal in order to achieve the desired path through the eye and achieve the advantageous results of the invention, which allow direct transmission of a higher power light beam will less risk to the retina compared to other technologies that use reflection.

Optical System

We assembled a flexible laboratory measurement system that is suitable both for calibration measurements as well as measurements on the eye. The system uses a standard monochrometer and incandescent light source to produce selected light wavelengths. The output of the monochrometer is coupled through fiber optics to miniature output lenses to produce collimated (parallel light) beams that are projected through standard cells for calibration or through the eye. The transmitted beam uses similar fiber coupling to send the transmitted beam to a detector to measure the transmitted light intensity. The monochrometer used for the experiments has the following characteristics:

Configuration:Off Axis Ebert-Fastie

Range:1.2 to 4 microns

Grating:300 lines/mm

Dispersion:25.6 nm/mm

Focal length:125 mm

Effective Aperture:F/3.7

Slit sizes50 to 1,000 microns

The use of fiber optic coupling is technically significant to these experiments since it permits rapid and simple adjustment of the optical measurement path to accommodate a

variety of experimental conditions. The lenses used are graded index (GRIN) lenses which have been specifically developed to couple light into and out of optical fibers. Figure 4a shows a schematic diagram of a GRIN lens coupled to an optical fiber.

To focus light and form an image, a lens must have the longest optical path at its center and shorter optical paths as the light ray moves radially outward. The standard lens accomplishes this by being thick in the center and thinner near the edges with a uniform index of refraction. The graded index lens accomplishes the same thing by having uniform length but lower index of refraction near the edges. This is the same principle used by graded index optical fiber in guiding light. The GRIN lens is made with the same technology that is used to make optical fiber, and lends itself well to coupling to fiber since it has a long thin shape and excellent rotational symmetry. Figure 4b shows a diagram of a lens-fiber assembly as a preferred embodiment.

GRIN lens and fiber assembly.

As can be seen from the drawing, the long thin shape makes it relatively simple to hold the lens in close proximity to the eye while allowing clearance for mounting and alignment hardware well away from the eye. For spectroscopic measurements of the aqueous humor we constructed a special fixture to hold the lenses as shown in Figure 5, which is a horizontal section through the skull and eyes. The lens holder was derived from goggles which closely fit the facial contour and provide a stable and reproducible alignment relative to the brow ridge, the cheek bone and the bridge of the nose. The input beam is projected from the outer side of the eye from an angle approximately 20 degrees behind the plane defined by the pupil. The subject fixates on a point directly in front of them so that the eyes are directed forward. Due to the symmetry of the eye, the exit angle

for the beam also lies approximately 20 degrees behind the same plane, as shown, and roughly is directed to strike the bridge of the nose. Since there is not enough volume between the exit point and the bridge of the nose to accommodate a lens, a small turning mirror is used to redirect the beam in a forward direction to the receiving lens location shown in the figure. The position of the mirror is fixed while both lenses have position adjustments to permit alignment of the complete optical system.

What Is Claimed Is:

1. A device for measuring blood glucose concentration, comprising an infra-red light source, a means for transferring light from the light source to enter the eye at a first location, a light detector that receives transmitted light from the eye at a second location after passing through a portion of the aqueous humour and that converts information from the light into an electrical signal, an electrical processor to convert the electrical signal into a value corresponding to blood glucose concentration, and a display to indicate the blood glucose value.

2. The device of claim 1, wherein the infra-red light source is selected from the group consisting of a light emitting diode, a laser diode, an incandescent lamp with a monochrometer, and an incandescent lamp with a fourier transform spectrometer.

3. The device of claim 1, wherein the means for transferring light from the light source to the eye is an optical fiber coupled to a gradient index lens.

4. The device of claim 1, wherein the means for transferring light from the light source to enter the eye at a first location directs the light at approximately a 70 degree angle of incidence with respect to the eye surface.

5. The device of claim 3, further comprising a second optical fiber coupled to a gradient index lens to collect light from the eye and transfer the collected light to the light detector.

6. The device of claim 1, wherein the detector is a semiconductor diode or a pyroelectric device.

7. The device of claim 1, wherein the processor comprises at least one bandpass filter and amplifier to process the electrical signal.

8. The device of claim 1, wherein the display is a liquid crystal.

9. The device of claim 1, wherein the device is hand-held.

10. Glasses that comprise a blood glucose sensor, the sensor comprising an infra-red light source, a means for transferring light from the light source to enter the eye at a first location, and a light detector that receives transmitted light from the eye at a second location after passing through a portion of the aqueous humour and that converts information from the light into an electrical signal corresponding to blood glucose concentration.

11. A system for controlling blood glucose comprising a device as claimed in claim 1 and a glucose pump, wherein the electrical signal of the device controls the glucose pump in response to changes in blood glucose concentration.

FIG. 1

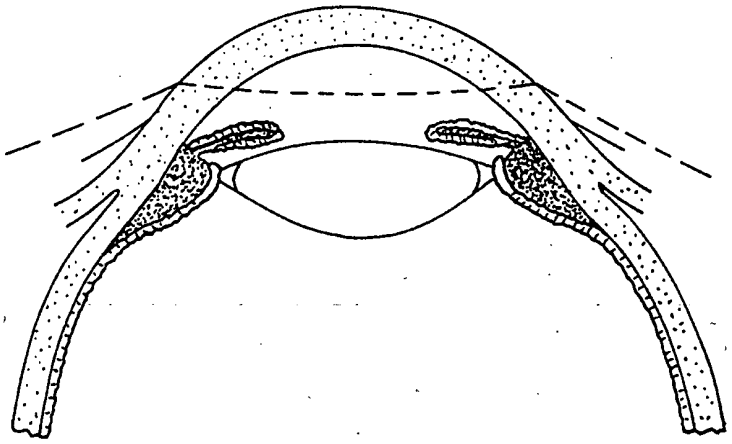


FIG. 2

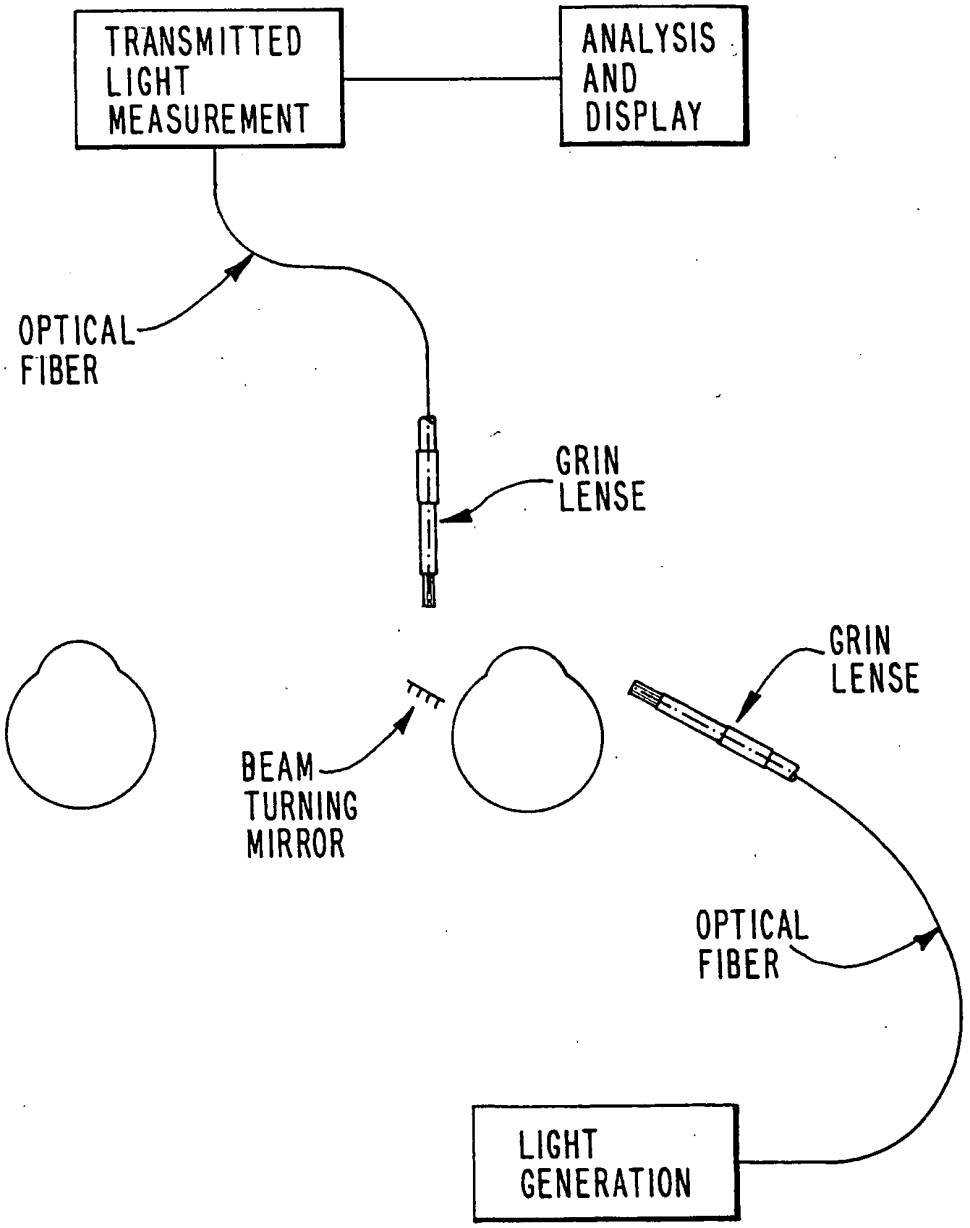

TRANSMITTED LIGHT MEASUREMENT
ANALYSIS AND DISPLAY
OPTICAL FIBER
GRIN LENSE
GRIN LENSE
BEAM TURNING MIRROR
OPTICAL FIBER
LIGHT GENERATION

FIG. 3

D-glucose linesSuitable for use

1198x

1269x

1371

1440

1493

1589

1705x

1750x

1789x

1834

2073

2103x

2200x

2275x

2330

2364

FIG. 4A

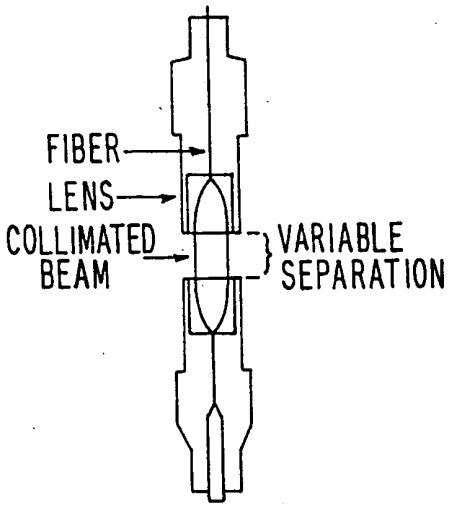

FIBER
LENS
COLLIMATED BEAM
VARIABLE SEPARATION

FIG. 4B

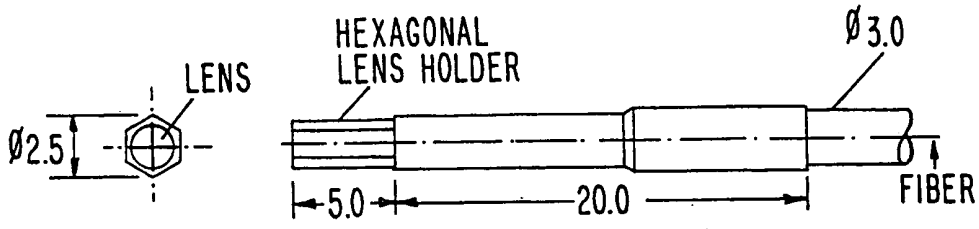

LENS
Ø2.5
HEXAGONAL LENS HOLDER
Ø3.0
5.0
20.0
FIBER

FIG. 5

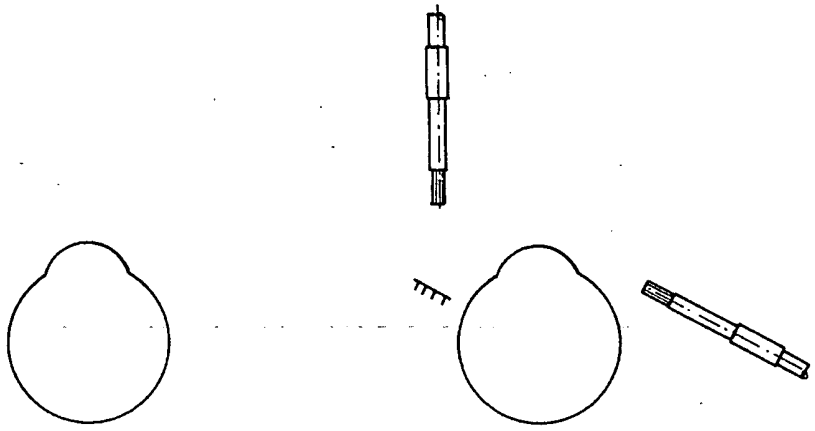


FIG. 6

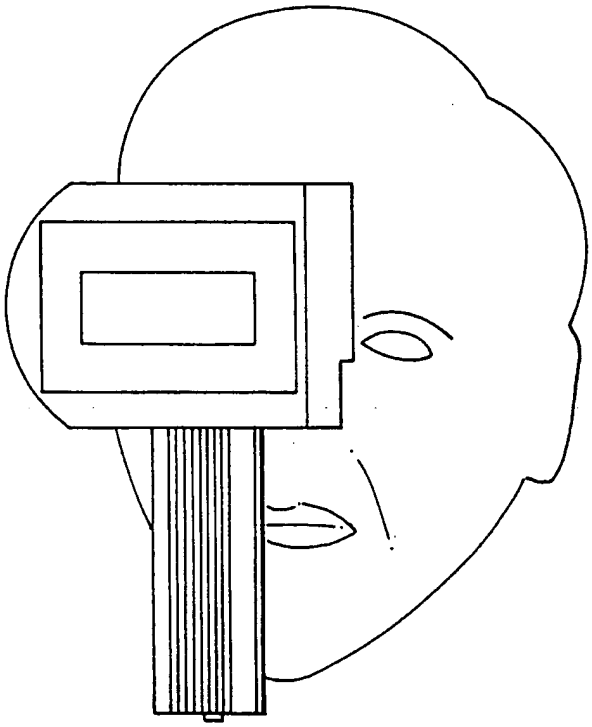
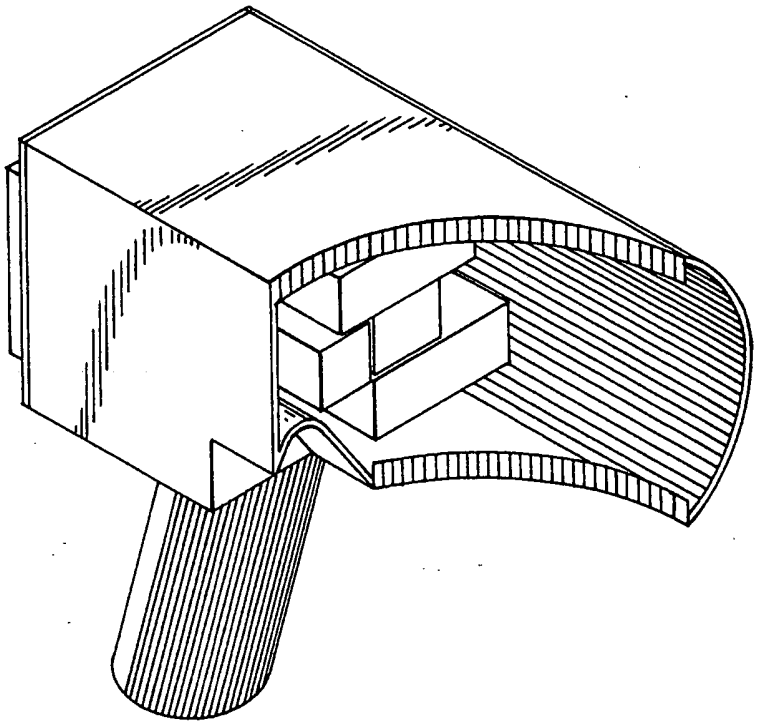


FIG. 7



INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 99/05007

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/00 A61B3/117

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 014 321 A (MARCH WAYNE F) 29 March 1977 cited in the application	1,2,4
Y	see column 1, line 63 - column 2, line 16 see column 2, line 51 - line 54 ---	3,5-10
Y	US 4 350 163 A (FORD JR NORMAN C ET AL) 21 September 1982 see column 1, line 16 - line 22 see column 1, line 62 - line 64 see column 2, line 54 - column 3, line 12; figure 1 --- -/--	3,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 June 1999	09/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Navas Montero, E

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INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 99/05007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 92 10131 A (GEORGIA TECH RES INST) 25 June 1992 see page 1, line 4 - line 10 see page 12, line 10 - line 29 see page 13, line 7 - line 24; figures 3,5	6,7
Y	WO 93 07801 A (SCIENT GENERICS LTD) 29 April 1993 see page 1, line 4 - line 9 see page 15, line 8 - line 27; figures 2-5	8,9
Y	EP 0 776 628 A (YOSHIDA AKITOSHI) 4 June 1997 see column 13, line 14 - line 31; figure 5	10
X	WO 92 07511 A (UNIV CONNECTICUT) 14 May 1992 see page 1, line 3 - line 9 see page 3, line 8 - line 26 see page 9, line 23 - page 10, line 2; figures 2,4	11

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